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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FALK, ANNE MARIE	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/813,203	SAH ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-17 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed September 23, 2008 (hereinafter referred to as "the response") has been entered. Claims 12-17 have been amended and Claim 33 has been newly added.

The elected invention is drawn to a method for introducing a CNS cell into a mammal and a method for treating a patient. Applicants further elected *v-myc* as the growth-promoting gene and Parkinson's disease as the elected disease species.

Claims 12-17 and 33 remain pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 12-17 stand rejected and Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for introducing a CNS cell into a mammal or other subject, wherein the CNS cell is prepared by a specified protocol that involves immortalization of the cell. The claims are further drawn to a method for treating a patient by administering a conditionally-immortalized clonal human CNS progenitor cell capable of differentiation into neurons and astrocytes.

The specification contemplates using genetically modified CNS progenitor cells in a method for treating a patient, including patients afflicted with Parkinson's disease. As such, the claimed invention is

directed to a method of *ex vivo* gene therapy. Such a method would involve transplanting or implanting isolated human neural progenitor cells into a human patient for treatment of a neurological or neurodegenerative disease or disorder. The success of the method relies on the engraftment, survival, and functional integration of the transplanted neural progenitor cells, as well as the biological effect of the transplanted cells on the region into which the cells are implanted.

At the time the invention was made, successful implementation of cell therapy protocols and *ex vivo* gene therapy protocols were not routinely achievable by those skilled in the art. At the time the application was filed, the art of administering transduced neural progenitor cells, to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable.

The following references are representative of the state of the art, at the time of the invention, as pertains to the transplantation of neural progenitor cells for therapy.

Rossi and Cattaneo (2002) acknowledge that "despite intense research activities and media attention, stem cell therapy for neurological disorders is still a distant goal" (abstract). The reference emphasizes the need for homogeneous populations of neural stem cells and the further need to understand the mechanisms required for "their proper integration into the injured brain" (abstract). The authors point out that "the functional integration of donor cells remains a highly demanding task that requires a profound understanding and control of the biological properties of both donor cells and the host environment" (page 401, column 2, paragraph 2, last sentence).

Cao et al. (2002) acknowledge the potential for the use of stem cells in therapeutic transplantation and for *in vivo* manipulation of endogenous precursors, but emphasize that "this at present is challenging and so far has been unsuccessful" (abstract and page 507, column 2, paragraph 2). The authors further point out that "[u]nderstanding mechanisms of NSC differentiation in the context of the injured CNS will be critical to achieving these therapeutic strategies" (abstract and page 507, column 2, paragraph 2).

Even under the best conditions, cell therapy in the central nervous system is highly unpredictable. For example, Milward et al. (1997) demonstrates that transplantation of neural stem cells (NSCs) to the CNS does not produce a therapeutic effect in a diseased animal. Milward et al. describes the transplantation of canine CNS NSCs into both rat and a shaking pup myelin mutant dog. In the rat, this resulted in the production of myelin by graft-derived cells. The authors report that the grafted cells integrated normally into the adult shaking pup cytoarchitecture. Yet despite all this, the clinical deficit of these animals was not ameliorated. Thus, it is clear that the production of myelin *in vivo* and normal integration of cells is not predictive of a therapeutic outcome. Given the unpredictability in the art of therapeutic transplantation, the development of therapeutic protocols requires substantial experimentation.

Mehler et al. (1999) disclose that many studies have suggested that the normal adult brain may lack the appropriate environmental signals to allow neural progenitors to realize their broad lineage potential. Specific neuropathologic conditions may alter the normal balance of regional environmental signals, for example by releasing proinflammatory and other modulatory cytokines. The presence of these inappropriate cellular cues may predispose residual neural populations to undergo apoptosis. The authors state that "[t]his suggests that it may be necessary to promote lineage commitment of progenitor cells *in vitro* prior to transplantation into a damaged brain" (p. 782, column 1, paragraph 1).

Numerous parameters act to determine the biological effect of a transplantation protocol. As noted above, the success of the method relies on the engraftment, survival, and functional integration of the transplanted neuronal progenitor cell, as well as the biological effect of the transplanted cells on the region into which the cells are implanted. The art further demonstrates that the route of administration of the cells to the individual is critical. Kennea et al. (2002, J. Pathology 197: 536-550) disclose that the precise site of injection can influence the fate of transplanted neural stem cells (page 545, column 2, paragraph 2) and that cell-cell interactions are likely to be important in determining the correct terminal differentiation of neural stem cells (page 545, column 1, paragraph 3). Furthermore, therapeutic

transplantation may be directed to treatment of diseases such as Parkinson's disease, Alzheimer's disease, demyelinating diseases, and other degenerative neurological diseases that involve an ongoing pathological process that may affect the fate of transplanted cells in a manner similar to its effect on endogenous neurons. For this reason, as well as the effects of the regional environment discussed above, the host environment is an important factor affecting the fate of transplanted cells.

In addition to the problems inherent to the therapeutic transplantation of neural progenitor cells, further obstacles are encountered in the gene therapy art. The disclosure is directed to using the human CNS progenitor cells in *ex vivo* gene therapy and therefore relies on the appropriate expression of a gene of interest for the overall success of such methods. Although the gene is introduced into the cell *ex vivo*, the continued expression of the gene in the *in vivo* environment is relied upon for the claimed method of the invention. However, gene therapy is not enabled for the reasons set forth below. The only utility asserted in the specification for the method as claimed, across the full scope, is for *ex vivo* gene therapy.

The claimed invention is directed to methods of gene therapy. However, gene therapy is not routinely successful. Therefore, the disclosure must enable the full scope of the claimed methods with specific guidance. However, the specification fails to adequately teach a method for using a cell as recited in the claims wherein the cell is transfected with an expression vector prior to transplantation, to produce a conditionally-immortalized human CNS progenitor cell for production of a therapeutic effect when transplanted into the patient. The specification does not provide specific guidance for the transplantation of recombinant CNS progenitor cells. At the time the application was filed, the art of administering any type of genetic expression vector to an individual so as to provide a tangible therapeutic benefit was poorly developed and unpredictable. The NIH ad hoc committee to assess the current status and promise of gene therapy reported in December 1995 that "clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims...," and that "significant problems remain in all basic aspects of gene therapy" (Orkin and Motulsky, p. 1). In a

review article published in Scientific American in June 1997, Theodore Friedmann discusses the technical barriers which have so far prevented successful gene therapy, and states "So far, however, no approach has definitively improved the health of a single one of the more than 2,000 patients who have enrolled in gene therapy trials worldwide" (p. 96). In a review article published in Nature in September 1997, Inder Verma states "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story" (p. 239). The instant specification does not adequately teach one skilled in the art how to use the claimed methods in various treatment protocols, for a variety of diseases, to produce a therapeutic effect.

Even as late as the year 2000, Grobhans (2000) cautions that even when the delivery and integration problems are solved, the requirement for stable expression still remains to be met and is normally prevented by a number of mechanisms, including the recognition of manipulated cells as foreign and their subsequent destruction b the immune system or the recognition of foreign regulatory sequences and subsequent shutdown by the cell (page 144, column 2, paragraph 3). Thus, absent any showing that the claimed methods can be used to produce the intended therapeutic effect in an immunocompetent animal, such as a human, rat, mouse, etc., the claimed invention is not enabled by the disclosure. As gene therapy is not routine for the reasons discussed herein, undue experimentation would have been required for one skilled in the art to practice the claimed method, particularly over the full scope, which is very broad.

The references raise concerns relating to cellular persistence and gene expression that are equally relevant to *ex vivo* gene therapy as for *in vivo* gene therapy. Furthermore, as noted above, successful integration and persistence of the transplanted cells is a critical problem facing all forms of cell therapy and particularly *ex vivo* gene therapy, which has the further problem of expressing a gene of interest in an appropriate tissue.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

In view of the quantity of experimentation necessary to determine appropriate parameters for using the claimed methods in therapeutic transplantation, and given the lack of applicable working examples, the limited guidance in the specification with regard to the use of different cells expressing different exogenous genes, the broad scope of the claims with regard to the type of gene to be used, the type of cell to be used, and the mode of administration, and the unpredictability in the cell therapy and gene therapy arts, undue experimentation would have been required for one skilled in the art to use the claimed methods in therapeutic protocols.

At pages 5-6 of the response, Applicants assert that the transplantation of conditionally-immortalized CNS progenitor cells results in site-specific differentiation. First, site-specific differentiation in a healthy adult or neonatal brain is not predictive of a therapeutic effect in a diseased brain, particularly for degenerative neurological diseases that involve an ongoing pathological process that may affect the fate of transplanted cells in a manner similar to its effect on endogenous neurons, as discussed in the rejection of record. Second, the references cited in the rejection of record teach that even when graft-derived cells integrate normally into the cytoarchitecture of a diseased brain, that normal

integration of cells is not predictive of a therapeutic outcome (see especially Milward et al., 1997). Thus, there is no evidence that transplanted cells that differentiate *in vivo* produce a therapeutic effect.

At page 7 of the response, Applicants assert that Renfranz et al. (1991), Snyder et al. (1992), Gao and Hatten (1994), and Shihabuddin et al. (1995) all demonstrate that immortalized cells have the developmental plasticity to respond to local microenvironmental signals and the adult brain retains the capacity to direct differentiation of these cells. Applicants cite Snyder (1992) for demonstrating that immortalized cell lines transformed by *v-myc* are capable of engraftment and differentiation into neurons or glia in a manner appropriate to their site of engraftment, where such cells could be identified in animals up to 22 months postengraftment. Applicants cite Gao and Hatten (1994) for demonstrating that immortalized cells, in contrast to primary external germ layer (EGL) cells, give rise to multiple types of cells after implantation, and that their findings are consistent with Renfranz et al. (1991), in that immortalized progenitor cells differentiated into a variety of cerebellar cell classes after early implantation. Applicants cite Shihabuddin et al. (1995) for demonstrating that immortalized cells showed consistent morphology within their transplantation site, and that immortalized cells have the developmental plasticity to respond to local microenvironment signals and that the adult brain retains the capacity to direct differentiation of neuronal precursor cells in a direction that is consistent with that of endogenous neurons. Applicants' arguments have been fully considered but are not deemed persuasive. In response, the studies of Snyder et al. (1992), while evaluating engraftment potential, survival, and developmental potential in healthy animals, do not address transplantation into diseased animals. Likewise, the studies of Gao and Hatten (1994), while examining questions of cell fate, do not address the issues pertaining to therapeutic transplantation, as their studies did not look at implantation of progenitor cells into diseased animals. Likewise, while the studies of Renfranz et al. (1991) looked at the developmental capacity of the hippocampal stem cell line HiB5, their studies do not address the issues pertaining to therapeutic transplantation, as they did not study implantation of the cells into diseased

animals. Likewise, Shihabuddin et al. (1995) did not look at implantation into the diseased brain, but rather only looked at developmental capacity in healthy animals. As discussed in the rejection of record, site-specific differentiation in a healthy adult or neonatal brain is not predictive of a therapeutic effect in a diseased brain, particularly for degenerative neurological diseases that involve an ongoing pathological process that may affect the fate of transplanted cells in a manner similar to its effect on endogenous neurons.

At page 7 of the response, Applicants assert that Trotter et al. (1993) demonstrate that immortalized cells may be used as transplants for demyelinating lesions in spinal cords of adult rats. However, while the abstract notes that early passages of the cells yielded myelin-forming oligodenrocytes and astrocytes, there is no evidence of a therapeutic effect in the animals. Furthermore, the present claims are not directed towards spinal cord administration or local administration to a demyelinated region of the CNS, which appears to be the protocol used to achieve development of myelin-synthesizing oligodendrocytes and astrocytes. Given the unpredictability in the art, the cited references do not demonstrate sufficient evidence of therapeutic transplantation for a protocol that falls within the scope of the claims, nor for the entire scope of the claims, which are directed to transplantation in subjects having a variety of pathological conditions. Applicants further cite Tuszynski et al. (1996) for demonstrating, in primates, that intraparenchymal grafts of genetically modified cells that produce NGF prevent neuronal degeneration. However, the result produced in that study was dependent on the production of NGF in a local region of the brain subject to surgical lesion (fornix transection). The experiment did not involve the use of immortalized CNS progenitor cells, but rather used fibroblasts genetically modified to produce NGF. However, the present claims are not directed to the use of cells genetically modified to produce NGF and there is no evidence in the cited reference that pertains to the use of immortalized CNS progenitor cells for therapeutic transplantation.

The rejection of record and the state of the art clearly establish unpredictability in the art of therapeutic transplantation. The unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman,* 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Here, the claims cover the treatment of patients having any pathological condition at all.

See also *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297 (CAFC 2005), which teaches: "[i]f mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

While the PTO bears the initial burden of providing reasons for doubting the objective truth of the statements made by Applicants as to the scope of enablement, when the PTO meets this burden, the burden shifts to applicant to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

Therefore, the claims remain rejected for reasons of record.

Conclusion

No claims are allowable.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632